REMARKS

Status of the Claims

Claims 1-11, 13-46, 58-62, and 64-68 are pending in the present application. Claims 2-11, 13-20, 32-46, 58-61, and 64 are withdrawn as directed to a non-elected invention. Claims 12 and 63 are presently canceled. Claims 47-57 were canceled by the preliminary amendment of August 2, 2006. Claim 1 is amended to incorporate the subject matter of canceled claim 12. Claim 62 is amended to incorporate the subject matter of canceled claim 63. Claims 21, 23, and 24 are amended to depend from pending claim 1. Claims 30 and 31 are amended to cancel the phrases the Examiner asserts are allegedly unclear. The claims are amended without prejudice or disclaimer. No new matter is entered by way of this amendment. Reconsideration is respectfully requested.

Rejection Under 35 U.S.C. § 102

Claims 1, 62, and 65-68 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Huang *et al.*, *Clinical Cancer Research*, 1998, 4: 2503-2509, ("Huang") or Chung *et al.*, *Clinical Cancer Research*, 2000, 6:1452-1458, ("Chung"), *see* Office Action, pages 3-4. Applicants respectfully traverse.

Independent claim 1, as amended, is directed to a pharmaceutical composition comprising at least one compound capable of enhancing gap-junction communication, at least one nucleoside analogue and a source of deoxyribonucleoside kinase.

Independent claim 62, as amended, is directed to pharmaceutical articles containing at least one nucleoside analogue, at least one compound capable of enhancing gap-junction communication and a source of deoxyribonucleoside kinase as a combination for the simultaneous, separate or successive administration in cancer therapy.

Huang describes the use of phenylbutyrate (PB) in connection with a nucleoside analogue for the treatment of cancer. Huang does not disclose that PB and a nucleoside analogue are used in combination with deoxyribonucleoside kinase.

Chung discloses PB and a nucleoside analogue for the treatment of cancer. Chung further links the activation of a thymidine kinase to the function of PB and the nucleoside

analogue. The thymidine kinase described in Chung is an endogenous kinase and, accordingly, is not a component in a pharmaceutical composition.

In view of the foregoing, the cited references do not teach all of the elements of the independent claims. Neither Huang nor Chung describes a pharmaceutical composition or pharmaceutical articles comprising or containing a compound capable of enhancing gap junction communication, a nucleoside analogue and a source of deoxyribonucleoside kinase. Accordingly, the cited references do not anticipate independent claims 1 and 62. Dependent claims 65-68, which incorporate all of the elements of independent claim 62, are also not anticipated by Huang or Chung. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

DiMartino, Yang and Lavie

Basis for the Rejection

Claims 1, 12, 21-31, 62-63, and 65-68 are rejected under 35 U.S.C. § 103 (a) as allegedly obvious over U.S. Patent No. 6,905,669 to DiMartino, ("DiMartino"), in view of U.S. Publication No. 20060068481 to Yang *et al.*, ("Yang"), and U.S. Publication No. 20070258968 to Lavie *et al.*, ("Lavie"), *see* Office Action, pages 4-7. Applicants respectfully traverse.

Specifically, the Examiner states that DiMartino describes compositions and methods for treating diseases associated with aberrant silencing of gene expression, such as cancer, by re-establishing gene expression through inhibition of DNA hypomethylation and histone deacetylase. The Examiner further states that DiMartino teaches that the DNA methylation inhibitor is a cytidine analog, such as decitabine. According to the Examiner, DiMartino teaches that, inside the cell, decitabine is first converted into its active form by deoxycytidine kinase.

The Examiner admits that DiMartino does not teach the delivery of a deoxyribonucleoside kinase to a cell via stem cell expression. However, according to the Examiner, Lavie and Yang remedy this deficiency. In particular, the Examiner states that Lavie describes methods for enhancing the efficiency of prodrugs by using specifically engineered enzymes with activity towards nucleoside analogs and delivering the enzymes to specific target cells in a patient. In addition, the Examiner states that Lavie describes modified deoxycytidine kinase.

The Examiner also states that Yang teaches human kinase nucleic acid sequences. According to the Examiner, Yang further teaches that, for ex vivo therapy, vectors may be introduced into stem cells taken from a patient and clonally propagated for autologous transplant back into that same patient.

In the Examiner's opinion, an ordinary artisan at the time of the invention would have modified the teachings of DiMartino with the teachings of Lavie and Lang to achieve the instant invention. According to the Examiner, DiMartino teaches compositions comprising deoxycytidine kinase and Lavie provides the nucleotide sequence of deoxycytidine kinase for exogenous expression. The Examiner further states that Yang teaches that kinases may be delivered into stem cells. Therefore, the Examiner believes that it would have been obvious to an ordinary artisan at the time of the invention to have substituted one means of delivering exogenous nucleic acids into cells for another delivery means, with the expectation of producing similar results.

The Present Invention

Independent claim 1 is directed a pharmaceutical composition comprising at least one compound capable of enhancing gap-junction communication, at least one nucleoside analogue and a source of deoxyribonucleoside kinase.

Independent claim 62 is directed to pharmaceutical articles containing at least one nucleoside analogue, at least one compound capable of enhancing gap-junction communication and a source of deoxyribonucleoside kinase as a combination for the simultaneous, separate or successive administration in cancer therapy.

The Cited References

DiMartino describes compositions containing PB and nucleoside analogues. The nucleoside analogues are administered in an inactive form and are, subsequently, converted into active forms inside the cell *via* a deoxycytidine kinase. The deoxycytidine kinase, as described in DiMartino, is an endogenous kinase. Accordingly, DiMartino does not teach or suggest a deoxycytidine kinase that is part of a pharmaceutical composition.

Lavie discloses a method for increasing the efficacy of prodrugs by using enzymes, such as deoxycytidine kinase, that have an affinity towards nucleoside analogues. Lavie further

describes methods for delivering the enzymes to a patient for use in treating cancer. Lavie does not teach or suggest the use of gap junction communication-enhancing compounds.

Yang describes human kinases and methods for delivering vectors into cells for use in cancer treatment. Yang does not teach or suggest the use of gap junction communication-enhancing compounds or the use of nucleoside analogues.

The cited references do not render the instant claims obvious

Initially, Applicants submit that none of the cited references teach or suggest a pharmaceutical composition or pharmaceutical articles that contain or comprise a compound capable of enhancing gap-junction communication, a nucleoside analogue and a source of deoxyribonucleoside kinase for cancer therapy. In addition, Applicants submit that the claimed pharmaceuticals result in effects that could not have been expected by an ordinary artisan at the time of the invention.

Applicants note that the present approach with suicide gene therapy, wherein an applied non-toxic nucleoside analog is converted to a cytotoxic compound by a kinase within a cell for use in cancer treatment, has a number of shortcomings. A major problem is the low rate of vector transduction of the tumor cells. Moreover, there is a restricted diffusion of activated (and thereby toxic) nucleoside analogues. This leads to an insufficient number of cancer cells being eradicated, thereby enabling continuous growth of the tumor.

In contrast, the claimed pharmaceutical composition has numerous and unexpected advantages. For example, an exogenously applied kinase may be delivered locally to the desired tumor area only. In addition, the kinase is selected for a specific purpose, and accordingly, a kinase may be selected that has high affinity towards particular nucleoside analogs. Thus, in this aspect, the claimed pharmaceutical composition is far superior to any endogenous kinase. Further, the addition of 4-PB, surprisingly, enhances the well known "bystander effect." This is an effect that is facilitated by gap junctions, which are formed between adjacent cells, allowing small molecules to diffuse freely. Thus, a small, toxic molecule having an effect in one cell can also have an effect in an adjacent cell, *i.e.*, a 'bystanding' cell.

Applicants would like to emphasize that an ordinary artisan at the time of the invention would not have known that 4-BP could have been used to enhance gap junction communication,

and, accordingly, enhance the bystander effect. It was not until the instant invention that this effect of 4-BP was recognized.

The present application provides strong evidence demonstrating that 4-PB clearly enhances gap junction communication and the bystander effect. This effect is demonstrated by observing an up regulation of the gap junction protein, Connexin 43, and by the increased flow of a dye from one cell to an adjacent cell, *see* Examples 1 and 2 in the originally filed application. Moreover, Applicants demonstrated that there is a clear relationship between the presence of a tomato deoxyribonucleoside kinase, which is exogenously applied, cell death, and the enhancement of cell death by 4-PB, *see* Figure 16 in the originally filed application.

In contrast to Applicants' recognition that 4-PB is effective as a gap junction communication enhancer, DiMartino teaches that PB is a histone deacetylase inhibitor, which is used to re-establish gene expression. In addition, Chung, which was further cited by the Examiner, describes PB as a protein kinase C modulator. None of these references teaches or suggests that PB functions as an enhancer of gap junction communication.

Applicants submit that, since the ability of 4-PB to enhance gap junction communication was unknown, it would not have been obvious to combine a nucleoside analogue, a dexoyribonucleoside kinase and a gap junction communication enhancer, such as 4-PB. This combination is not obvious. Furthermore, as described above, the combination of these three components provides unexpected advantages over the use of only two of the components.

In view of the foregoing, Applicants submit that the claims are not obvious in view of the cited references. Withdrawal of the rejection is respectfully requested.

Murphy, Gold and Jian

Claims 1, 12, 21-31, 62-63, and 65-68 are also rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Publication No. 2002-0049151 to Murphy *et al.*, ("Murphy"), in view of U.S. Patent No. 6,576,464 to Gold *et al.*, ("Gold"), and Jian Weiguo *et al.*, *Proceedings of the American Association Cancer Research Annual Meeting*, 2003, 44:1300-1301., ("Jian"), *see* Office Action, pages 7-8. Applicants respectfully traverse.

Murphy describes thymidine kinase in connection with a nucleoside analogue for cancer treatment. Murphy does not teach or suggest gap junction communication-enhancing compounds.

Gold discloses thymidine kinases in stem cells. In addition, Gold teaches a sequence of a thymidine kinase gene that is highly similar to SEQ ID NO: 3 of the present application. Gold does not teach or suggest the use of gap junction communication-enhancing compounds in cancer treatment.

According to the Examiner, Jian describes a combination of adenovirus mediated suicide gene therapy with the histone deacetylase inhibitors, butyrate and phenylbutyrate. Jian further describes administering this combination in vivo and in vitro.

As Applicants noted above, the instant invention results in advantages that would not have been expected by an ordinary artisan at the time of the invention. As Applicants further noted above, the addition of 4-PB, surprisingly, enhances the bystander effect. The use of 4-BP to enhance gap junction communication, and accordingly, enhance the bystander effect was not known until Applicants' invention.

In view of the foregoing unexpected effects, the claims are not obvious in view of the cited references. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 112, 2nd Paragraph

Claims 30-31 are rejected under 35 USC 112, second paragraph, as allegedly indefinite. Specifically, the Examiner asserts that that the phrase "for example" and "such as" renders the claim unclear. Claims 30 and 31 are amended to cancel the allegedly unclear phrases. Accordingly, Applicants believe that the rejection is overcome and respectfully request withdrawal.

CONCLUSION

In view of the above amendment and remarks, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact L. Parker, Registration No. at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

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